II. The Claims Are Not Obvious Over the Art

A Claims 27, 34-36, 38, 41, and 48-50 Are Not Obvious Over Kahn in View of Mullenbach

Claims 27, 34-36, 38, 41, and 48-50 stand rejected under 35 U.S.C. § 102(b)/103(a) as allegedly unpatentable over Kahn in view of Mullenbach *et al.*, UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988). (Office Action, Page 3.) Applicants traverse the rejection for the reasons of record, supplemented as follows.

1. Claims Are Not Obvious in View of an "Obvious to Try" Standard

The Examiner employs an impermissible "obvious to try" standard that does not support a finding of obviousness under 35 USC § 103. The Examiner has selected glutathione peroxidase from a large number (possibly thousands) of potentially useful expressed proteins known to one skilled in the art and combined it with "art recognized vectors" to reach the Applicants' claimed invention. Applicants contend that the Examiner employs an impermissible "obvious to try" standard in selecting and combining the cited publications. Accordingly, no *prima facie* case of obviousness can be shown.

The Federal Circuit in *In re O'Farrell*, 7 USPQ 2d 1673, 1681 (*Fed. Cir.* 1988) ("*O'Farrell*"), found that the Office had used an impermissible "obvious to try" standard in two main types of cases. In these cases, the Court found the claimed inventions to be non-obvious in view of the cited art.

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error.
>
> [(1)] In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, **where the**

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> **prior art gave** either no indication of which parameters were critical or **no direction as to which of many possible choices is likely to be successful**. . . .
>
> [(2)] In others, **what was "obvious to try" was to explore a new technology or general approach** that seemed to be a promising field of experimentation, **where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**

(*Id.*, emphasis, formatting and numbering added.) The Examiner's obviousness rejection of the current claimed invention violates both "obvious to try" standards described in *O'Farrell*.

The first "obvious to try" standard is violated when the Examiner selects Mullenbach from innumerable possible references disclosing DNA sequences encoding proteins. At the time the application was filed, one skilled in the art would not have found the claimed invention obvious from Kahn and McClelland unless the skilled artisan "[tried] each of numerous possible choices until one possibly arrived at a successful result" (*Id.*), namely selecting Mullenbach, where the prior art gave "no direction as to which of many possible choices is likely to be successful." (*Id.*) Kahn, McClelland and Mullenbach, either separately or apart, gave "no direction as to which of many possible choices is likely to be successful." (*Id.*) Essentially, the Examiner is arguing that it would have been "obvious to try" to modify Kahn or McClelland with Mullenbach under the first standard discussed in *O'Farrell*. Accordingly, combining Mullenbach with either Kahn or McClelland is impermissible to show *prima facie* obviousness. Applicants respectfully request that the Office reconsider and withdraw the rejection of Claims 27, 34-36, 38, 41, and 48-50 because a *prima facie* case of obviousness is not shown.

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The second "obvious to try" standard of *O'Farrell* is also violated in the present application because the teachings of Kahn and McClelland are, at most, only general guides as to the particular form of the claimed invention or how to achieve it. Non-obviousness of the claimed invention is supported by the second "obvious to try" standard of *O'Farrell* when the Examiner explores "a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." (*Id.*) Kahn and McClelland are, at most, only general guides as to teaching recombinant adenoviral vector expression of selected proteins. Kahn and McClelland give "only general guidance as to the particular form of the claimed invention or how to achieve it." (*Id*) There is no suggestion or guidance in the cited publications that glutathione peroxidase might be expressed by a recombinant adenoviral vector. Essentially, the Examiner is arguing that it would have also been "obvious to try" to modify Kahn or McClelland with Mullenbach under the second standard discussed in *O'Farrell*. Accordingly, combining Mullenbach with either Kahn or McClelland is impermissible to show *prima facie* obviousness. Applicants respectfully request that the Office reconsider and withdraw the rejection of Claims 27, 34-36, 38, 41, and 48-50 because a *prima facie* case of obviousness is not shown.

Applicants note that, while *O'Farrell* set forth the standard for determining "obvious to try", the Court found that the claimed invention in *O'Farrell* was obvious in view of the facts disclosed in Polisky, the cited art.

> [I]n Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly in terms of

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> transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

(*Id.*, page 1680.) The prior art disclosure cited in *O'Farrell* is distinguished from the cited publications in the present application. In *O'Farrell*, the Polisky reference explicitly suggested the substitution made by the Applicants and suggested the method could be used to make the polypeptide by presenting preliminary experimental evidence of the same. Unlike *O'Farrell*, the publications cited by the Examiner, Kahn and Mullenbach, suggest neither the ability, possibility nor desirability to express glutathione peroxidase in an adenoviral vector. In *O'Farrell*, the disclosure in Polisky supported a finding of obviousness under an "obvious to try" standard. Here, Kahn and Mullenbach do not support a finding of obviousness under an "obvious to try" standard as defined in *O'Farrell* .

Under the standard set forth in *O'Farrell*, as well as the other reasons expressed herein and in prior responses of record, the Office has failed to establish one of the three requirements for a *prima facie* case of obviousness. The mere fact that references can be combined does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Here, the desirability of the combination is found only in Applicants' specification. Accordingly, this rejection under 35 U.S.C. § 103(a) is improper and should be reconsidered and withdrawn.

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2. The Cited Cases Are Analogous to the Facts of the Present Application

The Applicants respectfully disagree with the Examiner's statement that

> [t]he arguments presented do not address this issue [of obviousness]. The present fact situation is not analogous to the fact situations in *In re Dembiczak* 50 USPQ2d 1614 (Fed. Cir. 1999); *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995); or *In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

(Office Action, page 4.) The fact situations of these cited cases are sufficiently analogous to the fact situation in the present application. Therefore, Applicants' recitation of these cases in this and prior responses of record is appropriate. Accordingly, Applicants submit that they have presented arguments which address and successfully traverse the Examiner's obviousness rejections.

In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991) is analogous to the fact situation in the present application because *Vaeck* and the present application both teach the use of a biological vector for expressing an encoded protein.

> In *In re Vaeck*, the chimeric gene of Dzelzkalns was designed to characterize promoters present in the chimeric gene, not to produce proteins encoded by the chimeric gene, as was the thrust of the invention being claimed; there was no motivation or suggestion to use an insecticidal protein as a reporter in place of CAT.

(Office Action, page 4.) The Office's statement is incorrect in view of the Dzelzkalns disclosure recited in *Vaeck* and the general knowledge of one skilled in the art.

> Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT)... Importantly, Dzelzkalns teaches the use of CAT gene as a "marker" gene; this use of antibiotic resistance conferring genes for selection purposes is a common technique in genetic engineering capable of being highly expressed in a cyanobacterium.

(*Vaeck*, pages 1440-1441.) The facts of *Vaeck* are analogous to the facts in the present application. The chimeric gene disclosed in Dzelzkalns was designed to

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express the CAT protein encoded by the CAT gene. It was known in the art that the CAT gene is purposefully and synthetically inserted into the bacterial genome so that the desired protein, CAT, could be expressed. The chimeric gene of Dzelzkalns was designed to express proteins encoded by the chimeric gene. Similarly, the adenovirus vector of the present claimed invention was designed to express a protein, glutathione peroxidase, encoded by an inserted gene. The secondary references in *Vaeck*, Sekar I, Sekar II and Ganesan, taught genes encoding insecticidally active proteins. Similarly, the secondary reference in the present application, Mullenbach, teaches a cDNA encoding glutathione peroxidase. In *Vaeck* the Federal Circuit found that "[t]he expression of antibiotic resistance-conferring genes in cyanobacteria, without more does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." (*Id.* at p. 1443.) In the present application, the expression of certain genes in an adenovirus vector for treating diseases of the central nervous system (disclosed in Kahn) does not render obvious the expression of an unrelated glutathione peroxidase gene (disclosed in Mullenbach) in the claimed inventive adenovirus vector for treating diseases of the central nervous system. The facts of *Vaeck* are analogous to the facts in the present application.

In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999) is analogous to the fact situation in the present application because neither the claimed invention in *Dembiczak* nor the present claimed invention is suggested in the publications or art of record cited by the Examiner.

> In *In re Dembiczak*, there was no suggestion in the prior art cited in the rejection to decorate trash bags in any way, let alone to decorate them as jack-o-lanterns as claimed. In the instant case, the adenoviral

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> vectors would have been used for their designed purpose, to express a desired protein.

(Office Action, pages 4 and 5.) As in *Dembiczak*, the publications cited against the present claimed invention were not properly combined. The Examiner contends that glutathione peroxidase, as suggested by Mullenbach, was "a desired protein", and therefore an obvious modification of Kahn. Applicants' have argued in responses of record that the only motivation to combine Kahn and Mullenbach comes from the Applicants' own specification. Furthermore, the Examiner' employs an impermissible "obvious to try" standard in combining the references, argued herein and in responses of record. Accordingly, as in *Dembiczak*, the Examiner has improperly combined the cited publications. Therefore, the Examiner cannot assert that Kahn and Mullenbach can be properly combined to suggest that the designed purpose of the adenoviral vectors is to express glutathione peroxidase.

In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995) is analogous to the fact situation in the present application because the claims in *Deuel* and the present application are both non-obvious over the generic teachings of the cited art because the cited art fails to suggest the claimed invention. The Examiner states the following:

> *In re Deuel* dealt with the issue of whether disclosure of a genus could anticipate a previously known species. This is not the case here, where the combination claimed is made up of parts (or subcombinations) previously known in the art.

(Office Action, page 5.) Applicants argue that the "parts" assembled by the Examiner were impermissibly combined, as discussed herein and in responses of record. The only motivation to combine the cited publications in the present application comes from the Applicants' own specification. There is no specific motivation in the cited publications to combine Mullenbach's disclosure of a

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glutathione peroxidase cDNA with the adenoviral vector teaching of Kahn. Accordingly, the issue discussed in *Deuel* of whether disclosure of a "genus" (e.g. a modified adenoviral vector in Kahn) could anticipate a "species" (e.g. a different adenoviral vector that expresses glutathione peroxidase) can be applied to the present application. Applicants submit that the holding in *Deuel*, that "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." (*Id.* at 1215) is readily applicable to the present application.

The facts of the present application are analogous to the facts in *In re Dembiczak*, *In re Deuel* and *In re Vaeck*. Accordingly, Applicants submit that they have presented arguments which address and successfully traverse the Examiner's obviousness rejections. Under the precedents set forth in these cited cases, as well as the other reasons expressed herein and in prior responses of record, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, this rejection under 35 U.S.C. § 103(a) is improper and should be reconsidered and withdrawn.

B. Claims 27, 34-36, 40, 41, and 48-50 Are Not Obvious Over McClelland in View of Mullenbach

Claims 27, 34-36, 40, 41, and 48-50 stand rejected under 35 U.S.C. § 102(e)/103(a) as allegedly unpatentable as allegedly unpatentable over U.S. Patent No. 5,543,328 to McClelland *et al.* ("McClelland") in view of Mullenbach. (Office Action, page 3.) The arguments traversing obviousness over Kahn in view of Mullenbach are herein incorporated by reference and applied to the Applicants' traversal of obviousness over McClelland in view of Mullenbach. Applicants traverse for the reasons of record, as well as those reasons discussed above, supplemented as follows.

The asserted teaching of Mullenbach has been discussed. McClelland is cited by the Examiner as disclosing "recombinant adenoviral vectors." (Office Action

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mailed January 21, 1998, page 21.) However, the adenoviral vectors in McClelland are different from the vectors in the present claimed invention. In particular, McClelland teaches adenoviral vectors comprising an adenovirus fiber protein that is covalently modified to include a required ligand which enables the adenovirus to be targeted to a desired cell type. McClelland does not teach the use of recombinant adenoviral vectors lacking covalently modified fiber proteins. The vector used in the current claimed invention is not taught or suggested by the uniquely modified adenoviral vector teaching of McClelland. Therefore, the Office has failed to make a *prima facie* case of obviousness because McClelland in view of Mullenbach does not teach or suggest all the limitations of the claims. See *In re Wilson*, 165 USPQ 494 (CCPA 1970). Accordingly, for this reason and reasons set forth in responses of record, the rejection is improper and should be reconsidered and withdrawn.

In addition, the Office admits that McClelland is also readily distinguished from the current application since McClelland "does not teach that glutathione peroxidase is a protein of interest." (Office Action mailed January 21, 1998, page 21.) For this teaching, Mullenbach is relied on, just as in the rejection involving Kahn.

Thus, this rejection suffers the same deficiencies as noted for the rejection over Kahn in view of Mullenbach. For the reasons set forth in reply to that rejection, the Office has not established a *prima facie* case of obviousness. No particular teaching, suggestion, or motivation to combine the teachings of McClelland and Mullenbach has been identified. Applicants request reconsideration and withdrawal of the rejection.

C. Claims 36, 38 and 50 Are Not Obvious Over McClelland and Mullenbach in view of Akli

Claims 36-38 and 50 stand rejected under 35 U.S.C. § 102(e)/103(a) as allegedly unpatentable over McClelland and Mullenbach, and further in view of *Akli*

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et al., Transfer of a foreign gene into the brain using adenovirus vectors, Nature Genetics, 3:224-28 (1993) ("Akli"). (Office Action, page 4.) The arguments traversing obviousness over Kahn or McClelland in view of Mullenbach are herein incorporated by reference and applied to the Applicants' traversal of obviousness over Kahn and McClelland and further in view of Akli. Applicants traverse for the reasons of record, as well as those reasons discussed above.

The Office has cited McClelland and Mullenbach as applied to claims 27, 28, 30, 31, 34-36, 39-41, and 48-50. (*Id.*, pages 8 and 9.) It states that this combination of references does not "teach that the DNA of interest could be operably linked to the RSV-LTR promoter or that glial cells could be infected. (Office Action mailed January 21, 1998, page 22.) To fill this gap, Akli is cited. (*Id.*) Akli, however, does not cure the deficiencies in the teachings of McClelland and Mullenbach.

As discussed by Applicants, the Office has not proffered any specific evidence that one of ordinary skill in the art would have been motivated to combine the teachings of McClelland and Mullenbach. Akli does not provide this motivation. Akli, according to the Office, merely teaches the use of an RSV-LTR promoter in adenoviral constructs and infection of glial cells by recombinant adenovirus. Hence, for the reasons set forth above, the claims are not *prima facie* obvious over the combined teaching of McClelland, Mullenbach, and Akli. Applicants request reconsideration and withdrawal of the rejection.

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SUMMARY

In view of the above remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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